

THE RECEPTOR TOXIN ANTIBODY INTERACTION: MATHEMATICAL MODEL AND NUMERICAL SIMULATION

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1 Introduction

An antibody, also known as an immunoglobulin, is a protein used by the immune system to identify, neutralize, or kill foreign objects like bacteria, viruses, or pollen which are termed as antigen. The production of antibodies is the main function of the immune system. An antigen, when introduced into the body, triggers the production of an antibody by immune system which will then kill or neutralize the antigen that is recognized as a foreign invader.

The bio-medical application of antibodies against an effect of toxins associated with various biological threats (epidemic outbreaks or bio-terrorism) is well-documented (see, e.g., [1–3]).

For a long time the main target of antibody design has been the antibody affinity. With progress in bio-engineering, many antibodies with different affinity parameters have been generated. However, according to Skvortsov and Gray [4] affinity is not a good predictor of protective or therapeutic potential of an antibody. In fact, the treatment effect of an antibody can be described by a parameter which includes the reaction rates of the receptor-toxin-antibody (RTA) kinetics and relative concentration of reacting species. As a result, any given value of this parameter determines a range of antibody kinetic properties and its relative concentration in order to achieve a desirable therapeutic effect.

The model considered by Skvortsov and Gray is a model of a well-mixed solution of toxin, antibody, and cells and neglects diffusion fluxes of interacting species. Diffusion fluxes are significant especially when the process of RTA interaction is limited by diffusion. Skakauskas et al. [5] examined numerically a RTA interaction model taking into account diffusion of all species in the case where a spherical cell is embedded into an initially uniformly distributed toxin–antibody solution which occupies a large volume (compartment) lying between the cell and external surface. Initial values of species and their values on the external surface were assumed to be the same for all times. In this case fluxes of toxin, antibody and their complex across the external surface are not zero. Some numerical results of the evaluation of an antibody treatment efficiency parameter are given in this paper.

In the present paper by using the same model we study the influence of RTA kinetic parameters and diffusivity of toxin, antibody, and their complex on the behavior of the antibody protection parameter and concentrations of species in more detail.

The paper is organized as follows. In Section 2 we introduce the reaction–diffusion model for RTA interaction. Numerical results are presented in Section 3. Summarizing remarks given in Section 4 conclude the paper.

2 The model

We study a case of a spherical cell embedded into a toxin–antibody solution which occupies an extracellular domain Ω lying between the cell and an external surface and use notations of paper [5]:

ρ – spherical radius,

$S_c = \{\rho : \rho = \rho_c\}$ – the surface of the spherical cell, ρ_c is its radius,

$S_e = \{\rho : \rho = \rho_e\}$ – the surface of the external sphere (external surface of Ω), ρ_e is its radius,

$\Omega = \{\rho : \rho \in (\rho_c, \rho_e)\}$ – the extracellular domain,

r_0 – the concentration of receptors on the cell surface,

$\theta(t, \rho)$ – the fraction of the toxin-bound receptors,

$r_0\theta$ – the concentration of the toxin-bound receptors (confined to S_c),

$r_0(1 - \theta)$ – the concentration of the free receptors,

u_T , u_A , and u_C – the concentrations of toxin, antibody, and toxin–antibody complex, respectively,

u_T^0 , u_A^0 , u_C^0 – the initial concentrations,

κ_T , κ_A , and κ_C – the diffusivity of the toxin, antibody, and toxin–antibody complex, respectively,
 k_1 , k_{-1} – the forward and reverse constants of the toxin–antibody reaction rate,
 k_2 and k_{-2} – the forward and reverse constants of the toxin and receptor binding rate,
 k_3 – the rate constant of the toxin internalization,
 ∂_n – the outward normal derivative on S_e or S_c ,
 $\partial_t = \partial/\partial t$,

$\Delta = \rho^{-2} \frac{\partial}{\partial \rho} (\rho^2 \frac{\partial}{\partial \rho})$ – the Laplace operator,

$\psi(t)$ – the antibody protection factor (a relative reduction of toxin inside a cell due to application of antibody).

Dynamics of the concentrations u_T , u_A , u_C , and θ can be described by the following equations:

$$\begin{cases} \partial_t u_T = -k_1 u_T u_A + k_{-1} u_C + \kappa_T \Delta u_T, & \rho \in \Omega, t > 0, \\ u_T = u_T^0, & \rho = \rho_e, t > 0, \\ \partial_n u_T = \frac{r_0}{\kappa_T} (-k_2(1-\theta)u_T + k_{-2}\theta), & \rho = \rho_c, t > 0, \\ u_T|_{t=0} = u_T^0, & \rho \in \Omega, \end{cases} \quad (1)$$

$$\begin{cases} \partial_t \theta = k_2(1-\theta)u_T - k_{-2}\theta - k_3\theta, & \rho = \rho_c, t > 0, \\ \theta|_{t=0} = 0, & \rho = \rho_c, \end{cases} \quad (2)$$

$$\begin{cases} \partial_t u_A = -k_1 u_T u_A + k_{-1} u_C + \kappa_A \Delta u_A, & \rho \in \Omega, t > 0, \\ u_A = u_A^0, & \rho = \rho_e, t > 0, \\ \partial_n u_A = 0, & \rho = \rho_c, t > 0, \\ u_A|_{t=0} = u_A^0, & \rho \in \Omega, \end{cases} \quad (3)$$

$$\begin{cases} \partial_t u_C = k_1 u_T u_A - k_{-1} u_C + \kappa_C \Delta u_C, & \rho \in \Omega, t > 0, \\ u_C = 0, & \rho = \rho_e, t > 0, \\ \partial_n u_C = 0, & \rho = \rho_c, t > 0, \\ u_C|_{t=0} = 0, & \rho \in \Omega. \end{cases} \quad (4)$$

The initial and boundary conditions for the system above correspond to a case where initially the toxin and antibody are distributed uniformly in the extracellular domain Ω . Values of all species on the outer boundary of Ω for all times and their initial values are assumed to be the same. In particular, zero value of the toxin–antibody complex is used for initial time and for all times on the outer boundary of Ω . We stress that in this case the fluxes of all species are not zero on the outer boundary S_e of Ω .

Eqs. (1)–(4) can be presented in non-dimensional form by using scales of τ_* (time), l (length), and u_* (concentration). By substituting variables $x = l\bar{x}$, $t = \tau_*\bar{t}$, $r_0 = lu_*\bar{r}_0$, $u_T = u_*\bar{u}_T$, $u_A = u_*\bar{u}_A$, $u_C = u_*\bar{u}_C$,

$u_{T0} = u_*\bar{u}_T^0$, $u_{A0} = u_*\bar{u}_A^0$, $\bar{k}_1 = \tau_*u_*k_1$, $\bar{k}_2 = \tau_*u_*k_2$, $\bar{k}_{-1} = \tau_*k_{-1}$, $\bar{k}_{-2} = \tau_*k_{-2}$, $\bar{k}_3 = \tau_*k_3$, $\bar{\kappa}_T = \tau_*\kappa_T l^{-2}$, $\bar{\kappa}_A = \tau_*\kappa_A l^{-2}$, $\bar{\kappa}_C = \tau_*\kappa_C l^{-2}$ into (1)–(4) we can deduce the same system, but only in the non-dimensional

variables. Therefore, for simplicity in what follows, we treat system (1)–(4) as non-dimensional.

The main antibody treatment efficiency parameter is the antibody protection factor (a relative reduction of toxin attached to a cell due to application of antibody) which can be defined by the following expression [4,5]:

$$\psi(t) = \frac{\int_{S_c} \theta|_{u_A^0 > 0} dS}{\int_{S_c} \theta|_{u_A^0 = 0} dS}. \quad (5)$$

By definition $0 \leq \psi \leq 1$. The lower the value of ψ the more profound is therapeutic effect of antibody treatment.

3 Numerical results

We treated system (1)–(4) numerically for the spherically symmetric domain, $\rho \in (\rho_c, \rho_e)$, and $t > 0$ with an implicit finite-difference scheme. Our selection of the values of parameters was motivated by the values available in the literature [3,5–7] with the extended range to allow exploration and illustration of the various transport and kinetics regimes that are possible in the RTA system. We employ the following data that were used in the most calculations in [5,8]: $u_* = 6.02 \cdot 10^{13} \text{ cm}^{-3}$, $\tau_* = 1 \text{ s}$, $r_0 = 1.6 \cdot 10^4 / S_c$, where $1.6 \cdot 10^4$ is the total number of

receptors of the cell, $l = 10^{-2}$ cm, $S_c = 4\pi\rho_c^2 = 4\pi \cdot 10^{-6}$ cm², $\bar{r}_0 = 2.115 \cdot 10^{-3}$. The standard non-dimensional values of the other parameters are the following:

$$\begin{cases} k_1 = 1.3 \cdot 10^{-2}, & k_{-1} = 1.4 \cdot 10^{-4}, \\ k_2 = 1.25 \cdot 10^{-2}, & k_{-2} = 5.2 \cdot 10^{-4}, & k_3 = 3.3 \cdot 10^{-5}, \\ \kappa_T = 10^{-2}, & \kappa_A = 10^{-2}, & \kappa_C = 10^{-2}, \\ \rho_e = 10^{-1}, & \rho_e = 2, \\ u_A^0 = 1, & u_T^0 = 0.5. \end{cases} \quad (6)$$

These values correspond to the ricin and 2B11 mono-clonal antibody interaction. If values of k_1 , k_2 , κ_A , κ_C , and κ_T differ from those given in (6), they are specified in the legends of plots.

As we indicated in the Introduction, the main purpose of our study was to estimate the effect of diffusive and kinetic parameters of species on the behavior of concentrations of species and protective properties of an antibody against a toxin. Results of numerical solving of system (1)–(4) are presented in Figs. 1–7.

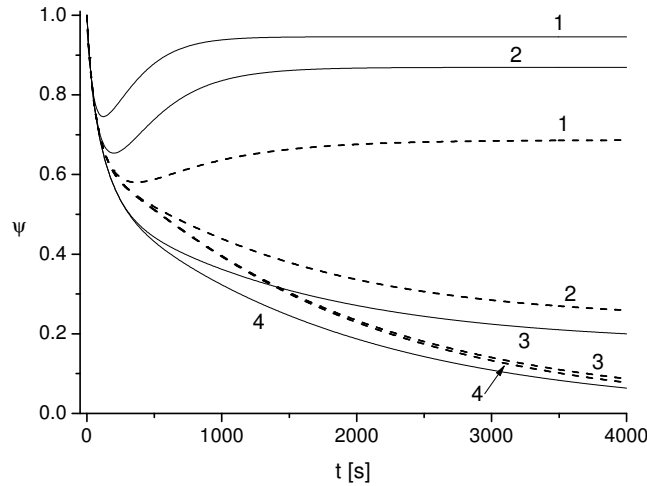


Fig. 1. Influence of the external radius $\rho_e = 2$ (solid line) and 5 (dashed line) and the toxin diffusivity $\kappa_T : 10^{-2}$ (1), $5 \cdot 10^{-3}$ (2), 10^{-3} (3), 10^{-4} (4) on the cell protection characteristic, ψ , in the case of $u_T^0 = 0.6$.

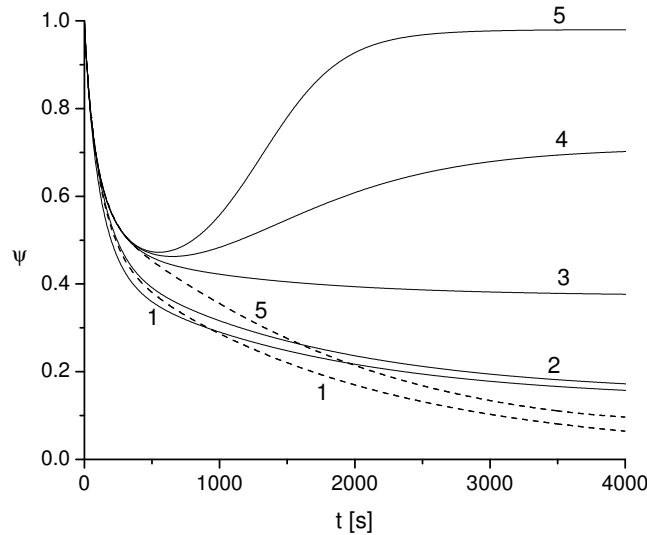


Fig. 2. Effect of the external radius $\rho_e = 2$ (solid line) and 5 (dashed line) and the antibody diffusivity $\kappa_A : 10^{-1}$ (1), 10^{-2} (2), 10^{-3} (3), $5 \cdot 10^{-4}$ (4), 10^{-4} (5) on the cell protection factor, ψ , in the case of $\kappa_T = 10^{-3}$.

The plots of ψ in Fig. 1 depict the dependence of the antibody protection factor on the radius ρ_e of the external surface S_e and toxin diffusivity κ_T . Parameter ψ increases with κ_T growing, but its behavior for large values of κ_T is non-monotonic. For large values of κ_T , parameter ψ grows as ρ_e decreases. But for small values of κ_T its behavior is different. For example, if $\kappa_T = 10^{-3}$, then values of ψ for $\rho_e = 5$ are larger than those for

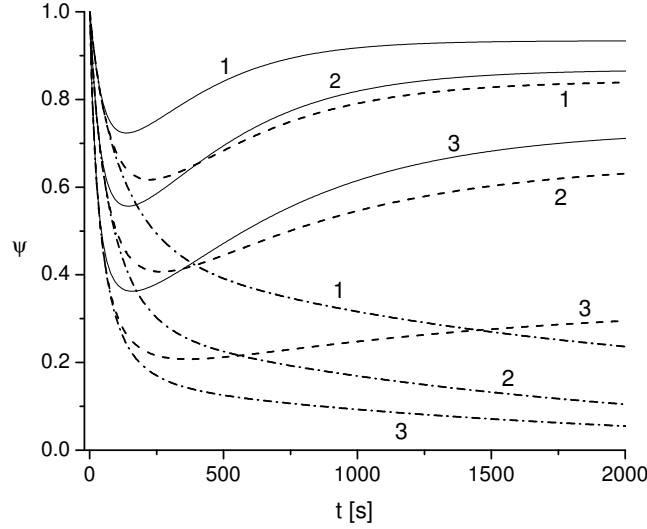


Fig. 3. Effect of the toxin diffusivity $\kappa_T : 10^{-2}$ (solid line), $5 \cdot 10^{-3}$ (dashed line), 10^{-3} (dash-dotted line) and parameter $k_1 : 1.3 \cdot 10^{-2}$ (1), $2 \times 1.3 \cdot 10^{-2}$ (2), $4 \times 1.3 \cdot 10^{-2}$ (3) on the cell protection function ψ .

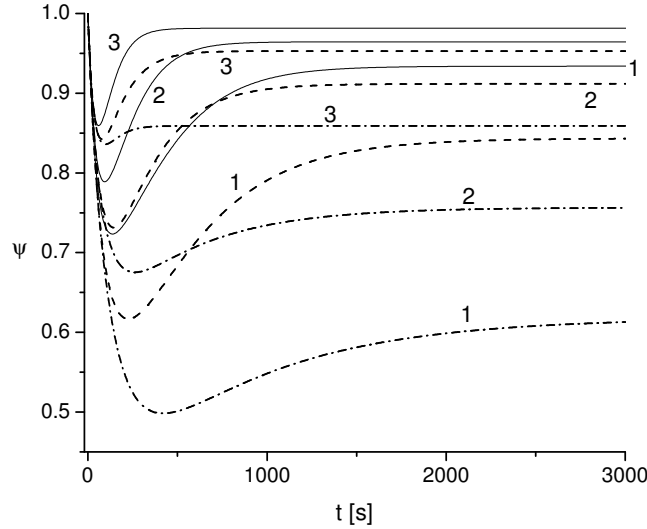


Fig. 4. Effect of the toxin diffusivity $\kappa_T : 10^{-2}$ (solid line), $5 \cdot 10^{-3}$ (dashed line), $2.5 \cdot 10^{-3}$ (dash-dotted line) and parameter $k_2 : 1.25 \cdot 10^{-2}$ (1), $2 \times 1.25 \cdot 10^{-2}$ (2), $4 \times 1.25 \cdot 10^{-2}$ (3) on the cell protection function ψ .

$\rho_e = 2$ if $t < 1400$ s approximately. But if $\kappa_T \leq 10^{-4}$, then, for all t , values of ψ for $\rho_e = 5$ are larger than those for $\rho_e = 2$ (see curves 3 and 4).

Fig. 2 illustrates the dependence of ψ on the diffusivity κ_A of the antibody. The curves in this figure depict the increase of ψ as κ_A decreases and non-monotonic time evolution of ψ for small values of κ_A . Moreover, in the case of small antibody diffusivity, $\kappa_A = 10^{-4}$, values of ψ for $\rho_e = 2$ are larger than those for $\rho_e = 5$. But in the case of large antibody diffusivity, $\kappa_A = 10^{-1}$, values of ψ for $\rho_e = 2$ are smaller than those for $\rho_e = 5$, only if $t \leq 1000$ s. For $t > 1000$ s they behave vica versa.

Figs. 3 and 4 exhibit the dependence of ψ on diffusivity κ_T , forward constant k_1 of the toxin and antibody reaction rate, and forward constant k_2 of the toxin and receptor binding rate, respectively. Fig. 3 demonstrates the decrease of ψ as k_1 increases. But different values of k_1 do not change the monotonic behavior of all curves in time. From Fig. 4 we see the non-monotonic behavior of ψ as k_2 increases. Moreover, ψ increases with k_2 increasing. The bottom of the hollow in Fig. 3 is located lower than that in Fig. 4. One can see in Fig. 4 that the effect of toxin diffusivity variation on protection factor is sensitive to changes of parameter k_2 . Let us compare the minimal values of protection factor. In the case of $k_2 = 1.25 \cdot 10^{-2}$, the minimum of ψ is about 0.72 at $\kappa_T = 10^{-2}$, 0.62 at $\kappa_T = 5 \cdot 10^{-3}$ and 0.5 at $\kappa_T = 2.5 \cdot 10^{-3}$, while the corresponding values of ψ are about 0.86, 0.84 and 0.836 in the case of $k_2 = 5 \cdot 10^{-2}$ (curves 1 and 3).

Numerical experiments show that diffusivity κ_C practically does not influence the time evaluation of ψ .

The plots of u_T in Fig. 5 depict the dependence of the toxin concentration at the cell surface on the diffusivity κ_T and radius ρ_e of the external surface S_e . For any value of ρ_e , u_T decreases with κ_T decreasing. For large

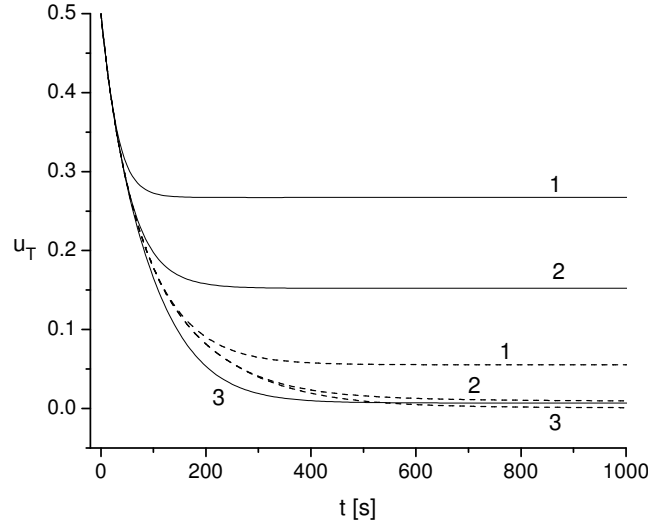


Fig. 5. Dynamics of toxin concentration u_T for $\rho_e = 2$ (solid line), $\rho_e = 5$ (dashed line), and $\kappa_T : 10^{-2}$ (1), $5 \cdot 10^{-3}$ (2), 10^{-3} (3).

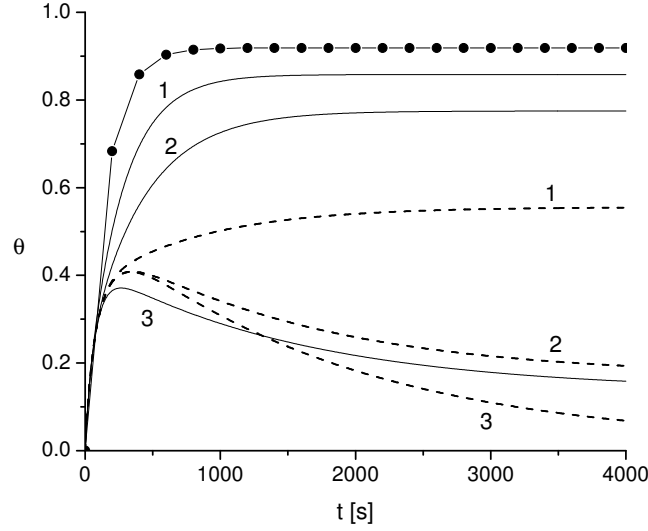


Fig. 6. Profiles of functions θ for $u_A^0 = 1$, $\rho_e = 2$ (solid line); $u_A^0 = 1$, $\rho_e = 5$ (dashed line), and $\kappa_T : 10^{-2}$ (1), $5 \cdot 10^{-3}$ (2), 10^{-3} (3). Line with bullets in the case of $u_A^0 = 0$.

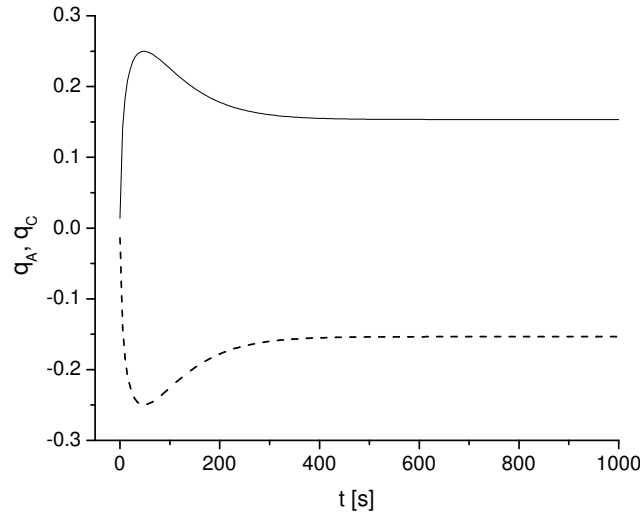


Fig. 7. Dynamics of functions $q_A = \partial u_A(t, \rho_e) / \partial \rho$ and $q_C = \partial u_C(t, \rho_e) / \partial \rho$ at $\rho_e = 2$ for $\kappa_T = 10^{-3}$ and $\kappa_A = \kappa_C = 10^{-2}$.

values of κ_T , function $u_T(t, \rho_c)$ grows as ρ_e decreases. But, for small values of κ_T , its behavior is different. For example, for $\kappa_T = 10^{-3}$, values of $u_T(t, \rho_c)$ for $\rho_e = 5$ are larger than those for $\rho_e = 2$ only if $t < 500$ s (see curves 3). Our calculations show that influence of κ_C on the behavior of $u_T(t, \rho_c)$ is insignificant. We observed the non-monotonic behavior of $u_T(t, \rho_c)$ for small κ_C , but difference between its steady-state value and value at the bottom of the hollow is very small (of order 10^{-3}).

Calculations show that $u_C(t, \rho_c)$ grows with κ_C decreasing. The behavior $u_C(t, \rho_c)$ is monotonic for $\kappa_C \leq 5 \cdot 10^{-2}$. Its values are smaller than initial ones of toxin for $\kappa_C \in [5 \cdot 10^{-3}, 5 \cdot 10^{-2}]$. But $u_C(t, \rho_c)$ can reach a relatively large steady-state value for small κ_C while steady-state values of u_T and u_A are smaller than their initial values. For example, the steady-state value of u_C on S_e is equal to 2.2 for $\kappa_C = 10^{-3}$, $\kappa_A = \kappa_T = 10^{-2}$. Derivatives of u_T and u_A with respect to ρ on S_e are of order 0.3 while derivative of u_C on S_e is of order -3 . This means that u_C increases faster towards the cell than u_T and u_A decays in the same direction.

Curves in Fig. 6 depict the dependence of θ on κ_T and ρ_e for $u_A^0 = 1$ and $u_A^0 = 0$. In the case where the antibody is absent values of θ practically do not depend on diffusivity κ_T (see the bullets marked curve). θ decreases with κ_T decreasing. For any ρ_e , function θ grows as κ_T increases. If $\kappa_T \in 5 \cdot [10^{-3}, 10^{-2}]$, then values of θ for $\rho_e = 2$ are larger than those for $\rho_e = 5$. But for small values of κ_T its behavior is different. For example, if $\kappa_T = 10^{-3}$, values of θ for $\rho_e = 5$ are larger than those for $\rho_e = 2$ only for about $t < 1300$ s. This behavior is similar to those of u_T and ψ .

Two curves in Fig. 7 illustrate the non-monotonic behavior of derivatives $\partial u_A(t, \rho_e)/\partial \rho$ and $\partial u_C(t, \rho_e)/\partial \rho$ for small toxin diffusivity ($\kappa_T = 10^{-3}$). For $\kappa_T = 10^{-2}$ their behavior is monotonic.

4 Concluding remarks

To conclude the paper we summarize results of study. The receptor–toxin–antibody interaction is studied numerically by using a model proposed in [5]. The model includes "bulk" reaction of toxin and antibody, surface binding of toxin and cell receptors, and diffusion of all species. The main results of the numerical study are the following:

1. The evolution of concentrations of some species (toxin and toxin-bound receptors) and of the antibody protection factor for some cases (large toxin diffusivity, small antibody diffusivity, and large forward constant of the toxin–receptor binding rate) is non-monotonic
2. The influence of small or large values of κ_T , κ_A , and k_2 on the behavior of $u_T(t, \rho_c)$, $\theta(t)$ and $\psi(t)$ is profoundly different in the cases of small or large ρ_e .
3. The effect of κ_C on the evolution of u_T , θ , and ψ was found to be insignificant.

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